



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
Detroit District Office
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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
2000-DT-04

December 2, 1999

Fred Hassan
Chief Executive Officer
Pharmacia & Upjohn Co.
100 Route 206 North
Peapack, New Jersey 07907

Dear Mr. Hassan:

A September 13 through September 24, 1999 inspection of your firm's aseptic drug manufacturing operations at your Kalamazoo, Michigan plant found that your firm is operating in serious violation of the Federal Food, Drug, and Cosmetic Act (the Act). During the inspection, our investigators documented numerous significant deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Part 211), which cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Act. While examples follow, we suggest you also refer to the list of inspectional observations which was issued at the conclusion of the inspection (copy enclosed) for additional details:

- 1) Failure to have a quality control unit adequate to perform its functions and responsibilities, as required by 21 CFR 211.22, as demonstrated by the number and types of inspectional observations. For example:
 - A) The quality control unit did not assure adequate validation of the HVAC system which supplies air to aseptic fill lines and did not detect that existing validation records do not document the operating conditions or equipment configurations used during validation.
 - B) The quality control unit did not conduct a thorough investigation of the drop in the air flow to the HEPA filters over aseptic fill line 1 between 4/2/99 and 8/25/99.

- C) The quality control unit did not assure that adequate systems and controls were in place to monitor the functioning of, and to detect malfunctions of, the air handling systems used to control and assure aseptic conditions in aseptic manufacturing areas.
 - D) The quality control unit did not sign/approve Procedure 00887 (Airflow Velocity Measurements of HEPA Filter), which describes the air velocity measurements in the aseptic fill area, and did not detect that this procedure lacks air velocity specifications.
 - E) The quality control unit did not detect that two different air flow velocity specification values were used on 1999 Pressure Drop Reports for Line 9.
 - F) The quality control unit did not review HEPA Bank test report findings for up to two months after the tests were performed and specifications/procedures had not been established to evaluate these test results.
 - G) The quality control unit did not assure that all areas used for aseptic manufacturing and processing operations are appropriately controlled and classified for their intended use.
 - H) The quality control unit did not assure that adequate controls were in place to assure that re-sterilized storage tank vent filters were appropriate for their intended use.
 - I) The quality control unit did not investigate, evaluate, and resolve all critical defects or discrepancies (in the number of contaminated vials found) during Sterile Process Simulation 634-08.
- 2) Failure of the quality control unit to conduct a thorough investigation and/or to make an adequate written record (including conclusions and follow-up) of such an investigation, as required by 21 CFR 211.192. For example, an adequate investigation was not conducted, and/or an adequate written record created, following the detection of the failure of the air handling system which supplied air to the HEPA filters over aseptic fill line 1 between 4/2/99 and 8/25/99.
- 3) Failure to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform their assigned functions, as required by 21 CFR 211.25. The observations made during this inspection indicate that personnel performing and/or supervising aseptic processing operations did not always possess the

knowledge to perform their assigned functions in such a manner as to provide assurance that aseptically filled drug products have the safety, identity, strength, quality, and purity they are purported or represented to possess. For example:

- A) Procedure 00887 was reviewed, approved and implemented despite the fact that it lacked air velocity specifications. Personnel reviewing, approving and implementing this procedure apparently did not notice or question this defect.
 - B) The HEPA Filter Reliability Maintenance Engineer, who was responsible for maintaining the air handling system to the aseptic processing areas, did not know the air handling system specification for air flow.
 - C) Sterile operation employees had not all participated in an annual media fill operation.
- 4) Failure to provide adequate air handling systems for aseptic processing, as required by 21 CFR 211.46. For example:
- A) There were no established specifications for air velocity at the HEPA filters which supply air to the aseptic fill lines.
 - B) The validation records for the performance of the HVAC system filters which supply air to aseptic filling lines 1, 8 and 9 did not document the system operating conditions during validation.
 - C) There was no system in place to detect and/or report malfunctions of the air handling systems used to control aseptic conditions.
 - D) The air flow supplied to the HEPA filters over aseptic filling line 1 dropped significantly sometime between 4/2/99 and 8/25/99; but, the drop was not detected and corrected at the time of occurrence.
 - E) The primary barriers used on aseptic fill line 8 were altered. Written procedures describing how such a change is to occur were not available and there is no assurance that the change did not affect the adequacy of the air handling system to the line.
- 5) Failure to have adequately designed procedures for production and process control to assure that aseptic drug products have the identity, strength, quality, and purity they purport or are represented to possess, as required by 21 CFR 211.100. For example:

- A) Trays of unstoppered and lyo-stoppered vials of sterile drug products were loaded into, and removed from, lyophilizers in areas that were classified and maintained as class 1000 rooms. Data was not available to show that all lyophilizer rooms had been tested to verify that they meet class 1000 conditions. Validation data was not available for the HVAC system in all lyophilizer rooms.
 - B) Open and upright sterilized vials move through the vial tunnel on aseptic filling line 8. The written procedure for this tunnel allowed up to 100,000 particles 5 microns or larger per cubic foot of air in the cooling area of the tunnel.
 - C) Written procedures did not contain instructions for the disposition of products remaining on an aseptic fill line during line stoppage.
- 6) Failure to have adequate control systems for aseptic processing to prevent contamination, as required by 21 CFR 211.42. For example:
- A) The system for monitoring environmental conditions did not detect a drop in the air flow supplied to the HEPA filters over aseptic filling line 1 sometime between 4/2/99 and 8/25/99.
 - B) There was no system in place to alert personnel of malfunctions of the air handling systems used to control aseptic conditions.
- 7) Failure to have batch production and control records which include complete information relating to the production and control of each batch, as required by 21 CFR 211.188. For example:
- A) Batch records did not identify the individuals who performed the 100% inspection of the filled vials.
 - B) The reason for production downtime was not documented in the relevant batch production records.
- 8) Failure to have a written record of major equipment cleaning, as required by 21 CFR 211.182. For example: the daily cleaning and sanitizing of the aseptic fill lines was not documented.
- 9) Failure to have and to follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures, as required by 21 CFR 211.84. For example:

Page 5
Warning Letter 2000-DT-4
Pharmacia & Upjohn
Peapack, NJ 07907

- A) [REDACTED] raw material lot 0213G and [REDACTED] lot 0430G were not identity tested prior to release to production.
- B) Raw material sampling records did not indicate how many containers were sampled or the amount of material removed from each container.

The above list of deviations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Good Manufacturing Practice Regulations. Other Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

We request that you take prompt action to correct these deviations and to ensure that your drug manufacturing systems are in full compliance with the Act and regulations promulgated thereunder. Failure to make prompt corrections may result in regulatory action without further notice, such as seizure and/or injunction.

We acknowledge receipt of your various written and verbal responses to the list of inspectional observations and your commitments to take specific steps to both correct the noted violations, and to make systemic corrections to assure that similar violations will not recur. We concur in your decision to seek the assistance of outside expertise to make the necessary corrections.


We note that your firm has committed to providing data sufficient to demonstrate that environmental control was maintained on specific lots of finished products during the time frame of the air flow failure (or the time frame during which the status of the air flow was unknown) and that the air flow failure did not affect product quality. Please provide this information in writing within ten (10) working days of your receipt of this letter. If the data cannot be submitted within 10 working days, please state the reason for the delay and the time frame within which the data will be submitted.

We realize that Pharmacia & Upjohn Co. has multiple locations. This letter is an official notification that FDA expects all of your locations to be in compliance. We recommend that all of your locations be evaluated and that corrective action be taken corporate-wide if deficiencies are found.

Page 6
Warning Letter 2000-DT-4
Pharmacia & Upjohn
Peapack, NJ 07907

Any additional reply concerning this matter should be directed to Sandra Williams, Compliance Officer, at the above address.

Sincerely,

A handwritten signature in black ink, appearing to read "Raymond V. Mlecko", with a small mark to the right.

Raymond V. Mlecko
District Director
Detroit District

Enclosure: FDA 483 dtd. 9/13-24/99
cc via certified mail:

R. Michael Enzinger, Ph.D.
Vice President, Kalamazoo Pharmaceutical Operations
Pharmacia & Upjohn Co.
7000 Portage Road
Kalamazoo, Michigan 49001